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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/623,329	11/13/2000	Marcel Bartolina Hendrikus Johannes Vervoort M.B.H.J.	T/98362 US	3850

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EXAMINER
MYERS, CARLA J

ART UNIT	PAPER NUMBER
1634	

DATE MAILED: 06/04/2002

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/623,329	VERVOORT M.B.H.J. ET AL.	
	Examiner	Art Unit	
	Carla Myers	1634	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *12 April 2002* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *15-26* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *15-26* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) 5 .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

1. Applicant's election with traverse of Group I in Paper No. 14 is acknowledged. The traversal is on the ground(s) that it would not require undue burden to concurrently search the LMP-2 sequences in addition to BKRF1/EBNA sequences because step 1 of the claimed invention is a general step of determining the presence of EBV infected cells and the second step (detection of BARF1) of the claimed method determines the specific EBV associated disease. This argument is not persuasive because examination of claims directed to detecting LMP-2 nucleic acids requires a separate, distinct search of LMP-2 nucleic acid sequences. A search of BKRF1/EBNA-1 sequences from nucleotides 10795-109872, of SEQ ID NO: 22-26 and of methods for detecting EBV epithelial tumor cells by assaying for BKRF1/EBNA-1 is clearly NOT co-extensive with, and does not provide all references obtained by, a search of LMP-2 sequences spanning exons 2-8, the specifically claimed LMP-2 primer and probe sequences, or a method for detecting EBV epithelial tumor cells by assaying for LMP-2. Applicants further argue that once the sequences of claim 19 are found to be novel and unobvious, then any sequences recited in claims which depend from claim 19 should also be found to be novel and unobvious. For these reasons, Applicants believe that examination of all of the claimed sequences would not require undue burden. However, as detailed below the sequences of claim 19 are NOT novel and unobvious and therefore the restriction is maintained. Clearly a search of any one single 10 mer fragment within nucleotides 107950-109872 of EBNA-1 (for which a nucleotide sequences is not provided) or for any one single 10 mer fragment within nucleotides 165504-166166 of the EBV genome (for which, again, a specific nucleotide sequence is not

provided) is very distinct from a sequence search of SEQ ID NO: 1, 2, 3, 4, 5, 22, 23, 24, 25 and 26. A search of each and everyone of these nucleotide sequences would require undue burden and thereby the restriction is maintained. The claims have been examined to the extent that they are limited to methods which detect EBNA-1 and BARF-1 sequences and to the primers of SEQ ID NO: 2 and 3 and probe of SEQ ID NO: 5 for the detection of EBNA-1 and the primers of SEQ ID NO: 23 and 24 and the probe of SEQ ID NO: 26 for the detection of BARF-1.

The requirement is still deemed proper and is therefore made FINAL.

2. This application contains sequence disclosures that are encompassed by the definitions for nucleotide and/or amino acid sequences set forth in 37 CFR 1.821(a)(1) and (a)(2). However, this application fails to comply with the requirements of 37 CFR 1.821-1.825 because the previously submitted Sequence Listing does not include all of the sequences recited in the specification. Specifically, the Sequence Listing does not include the sequence of the T7 polymerase promoter. See, for example, claims 16 and 23. As the sequence of the T7 polymerase promoter is well known in the art, this subject matter have been examined. However, compliance with the Sequence Rules require that all sequences set forth in the specification must be included in the Sequence Listing and that all recited sequences be accompanied by the appropriate sequence identifier. Accordingly, Applicant is required to submit a new CRF and paper copy of the Sequence Listing containing these sequences, in addition to the previously listed sequences, an amendment directing the entry of the Sequence Listing into the specification, an amendment directing the insertion of the SEQ ID NOs into the

appropriate pages of the specification/claims and a letter stating that the content of the paper and computer readable copies are the same.

3. The disclosure is objected to because of the following informalities:

A. In claim 15, "fro" should read "from".

B. Claims 25 and 26 are objected to because claim 25 does not properly depend from claim 15 since a claim to a product can not depend from a method of using a product (SEE MPEP 608.01(n)).

C. Claims 20, 23 and 24 should be amended to refer to a proper Markush group. That is, the claims should be amended to recite "selected from the group consisting of...**and**...", rather than "selected from the group consisting of....or..." See MPEP 2173.05(h).

4. Claims 15-18 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for methods for detecting EBV positive NPC or gastric carcinoma cells comprising amplifying and detecting the presence of BKRF1 sequences (from the region of 107950-109872) and BARF-1 sequences (from the region of 165504-166166) as indicative of the presence of an EBV positive NPC or gastric carcinoma cell, does not reasonably provide enablement for methods which detect any EBV positive epithelial tumor cell. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

The following factors have been considered in formulating this rejection (*In re Wands,* 858F.2d 731, 8 USPQ2d 1400 (Fed. Cir. 1988): the breadth of the claims, the nature of the

invention, the state of the prior art, the relative skill of those in the art, the predictability or unpredictability of the art, the amount of direction or guidance presented, the presence or absence of working examples of the invention and the quantity of experimentation necessary.

The claims are drawn broadly to methods for detecting the presence of an EBV-positive epithelial tumor cell. The specification (examples 5 and 7) teaches that BARF-1 is expressed in nasopharyngeal carcinoma (NPC) and gastric cancer. The specification also teaches that BARF-1 is not expressed in T cell non-Hodgkin lymphoma or Hodgkin lymphoma. Accordingly, the specification has enabled methods for detecting EBV positive NPC or gastric carcinoma cells comprising amplifying and detecting the presence of BKRF1 sequences and BARF-1 sequences as indicative of the presence of an EBV positive NPC or gastric carcinoma cells. However, the specification has not enabled the detection of any EBV positive epithelial tumor cell because the specification has not established that all, or a representative number of epithelial tumor cells express BARF-1. The specification (e.g. page 2) teaches that different gene transcription patterns are observed in different EBV associated malignancies. The specification (page 4) emphasizes the need to accurately determine the type and level of EBV gene expression in order to effectively diagnose EBV-associated malignancies. Accordingly, it is unpredictable as to whether the results obtained with NPC and gastric cancer can be extrapolated to other epithelial cancers. The specification has not established a correlation between BARF-1 expression and the occurrence of all types of epithelial cancers. Case law has established that "(t)o be enabling, the specification of a patent must teach those skilled in the art how to make and use the full scope of

the claimed invention without 'undue experimentation.'" *In re Wright* 990 F.2d 1557, 1561. *In re Fisher,* 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970) it was determined that "(t)he scope of the claims must bear a reasonable correlation to the scope of enablement provided by the specification to persons of ordinary skill in the art". The amount of guidance needed to enable the invention is related to the amount of knowledge in the art as well as the predictability in the art Furthermore, the Court in *Genetech Inc. v Novo Nordisk* 42 USPQ2d 1001 held that "(I)t is the specification, not the knowledge of one skilled in the art that must supply the novel aspects of the invention in order to constitute adequate enablement". In view of the high level of unpredictability in the art and the lack of guidance provided by the specification, undue experimentation would be required to practice the invention as it is broadly claimed.

5. Claims 15-26 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 15-18 are vague and indefinite because the claims are drawn to a method for determining the presence of EBV-positive epithelial tumor cells, yet recite only steps of determining the presence of EBV positive cells by amplifying BKRF1 RNA sequences and amplifying BARF1 reading frame sequences. It is noted that the claims do not include a step of detecting the amplified EBNA-1 or BARF-1 nucleic acids. The claims do not clearly set forth how the step of amplifying BARF1 reading frame sequences results in the identification of EBV-

positive epithelial tumor cells or how the step of amplifying EBNA-1 results in the identification of EBV positive cells.

Claim 16 is indefinite over the recitation of "the pairs of oligonucleotides" because this phrase lacks proper antecedent basis since the claim does not previously refer to pairs of oligonucleotides. This rejection may be overcome by amendment of the claim to recite, for example, "wherein the step of amplifying said RNA is performed using a pair of oligonucleotides selected form the group consisting of".

Claims 16 and 23 are indefinite over the recitation of "provided with a T7 promoter sequence" because it is not clear as to whether the T7 promoter sequence is provided separately with the pair of oligonucleotides or whether one or both of the primers further comprises the T7 promoter sequence.

Claims 19-22 and 24-26 are indefinite over the recitation of "corresponding" because this is not an art recognized term to describe the relationship between two nucleic acid sequences. It is not clear whether this refers to sequence homology/similarity or to sequence complementarity and it is not clear what percentage of homology or complementarity is encompassed by "corresponding" or under what types of conditions "corresponding" nucleotides are determined. For example, it is unclear as to whether "corresponding" is intended to be equivalent to "consisting of", "complementary to", "similar to", etc.

Claim 25 is indefinite over the phrase "substantially complementary". The specification does not provide a definition for this phrase and there is no art recognized definition for the term

"substantially". Accordingly, it is unclear as to what level of complementarity would be encompassed by "substantially complementary".

Claim 25 is indefinite over the recitation of "the amplified nucleic acid sequence" because this phrase lacks proper antecedent basis. Since claim 25 is drawn to a product, the claim does not include any method steps of amplification and thereby it is unclear as to what constitutes the amplified nucleic acid sequence.

Claim 26 is indefinite over the recitation of "test kit according to claim 24" because claim 24 is not drawn to a test kit. It appears that claim 26 should be amended to refer back to claim 25.

6. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless -
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claim 19 is rejected under 35 U.S.C. 102(b) as being anticipated by Cheung (reference "AM").

Cheung teaches primers of 19-21 nucleotides for amplifying BKRF1 reading frame sequences spanning nucleotides within the EBV region of nucleotides 107950-109872 (see page 785). Accordingly, the claimed invention is anticipated by the primers of Cheung.

7. Claims 19 and 20 are rejected under 35 U.S.C. 102(a) as being anticipated by Myers (GenBank Accession No.G34340).

Myers teaches a primer consisting of 5'-GGCTGTCACCCAGGTAGAAA-3'. The primer comprises at least 10 nucleotides of SEQ ID NO: 23 (i.e., nucleotides GGCTGTCACC). Furthermore, the claims are inclusive of sequences sharing any level of sequence complementarity to the oligonucleotides SEQ ID NO: 2, 3, 23 or 24 and the primers of Myers share some level of sequence complementarity with said oligonucleotides. This second aspect of the rejection may be overcome by amendment of the claim to recite "and sequences fully complementary thereto".

8. Claim 19 is rejected under 35 U.S.C. 102(a) as being anticipated by Myers (GenBank Accession No.G29936).

Myers teaches a primer consisting of 5'-TTTAAACTGGTAGGAAACTAGGTG-3'. The primer comprises at least 10 nucleotides of SEQ ID NO: 26 (i.e., nucleotides TTTAAACTGG). Accordingly, Myers teaches a primer/oligonucleotide comprising at least 10 nucleotides within the sequence of nucleotides 165504-166166 of BARF-1.

9. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claim 25 is rejected under 35 U.S.C. 103(a) as being unpatentable over Cheung. Cheung teaches primers of 19-21 nucleotides for amplifying BKRF1 reading frame sequences spanning nucleotides within the EBV region of nucleotides 107950-109872 (see page 785). Cheung further teaches labeled probes for detecting nucleic acids amplified by said primers (see page 786). Cheung does not teach packaging the primers and probe in a kit. However, reagent kits for performing diagnostic methods were conventional in the field of molecular biology at the time the invention was made. Therefore, it would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have packaged the primers and probe of Cheung in a kit for the expected benefits of convenience and cost-effectiveness for practioners in the art wishing to detect EBV BKRF1 sequences.

10. Claim 24 is rejected under 35 U.S.C. 103(a) as being unpatentable over Myers (GenBank Accession No.G29936).

Myers teaches a primer consisting of 5'-TTTAAACTGGTAGGAAACTAGGTG-3'. The primer comprises at least 10 nucleotides of SEQ ID NO: 26 (i.e., nucleotides TTTAAACTGG). Myers does not teach labeling the oligonucleotide primer.

Mullis (e.g., column 23) teaches labeling primers for use in PCR in order to facilitate the detecting of PCR amplification products.

Accordingly, it would have been obvious to one of ordinary skill in the art at the time the invention was made to have labeled the primers of Myers in order to have achieved the benefits .

11. Claim 21 is rejected under 35 U.S.C. 103(a) as being unpatentable over Cheung in view of Kievits (reference 'AO').

Cheung teaches primers of 19-21 nucleotides for amplifying BKRF1 reading frame sequences spanning nucleotides within the EBV region of nucleotides 107950-109872 (see page 785). Cheung further teaches labeled probes for detecting nucleic acids amplified by said primers (see page 786). Cheung does not teach incorporating a T7 polymerase promoter sequence into said primers.

Kievits teaches methods for amplifying nucleic acids by an isothermal enzymatic process referred to as NASAB. In this method, the primers are modified to include, at their 5' terminus, a T7 polymerase promoter sequence.

In view of the teachings of Kievits, it would have been obvious to one of ordinary skill in the art at the time the invention was made to have modified the primers of Cheung so as to have

included a T7 polymerase promoter at the 5' terminus in order to have generated primers which could be used to effectively amplify target nucleic acids by the NASAB method.

Accordingly, it would have been obvious to one of ordinary skill in the art at the time the invention was made to have labeled the primers of Myers in order to have achieved the benefits stated by Mullis of facilitating the detecting of PCR amplification products.

12. Claims 21 and 22 are rejected under 35 U.S.C. 103(a) as being unpatentable over by Myers (GenBank Accession No.G34340).

Myers teaches a primer consisting of 5'-GGCTGTCACCCAGGTAGAAA-3'. The primer comprises at least 10 nucleotides of SEQ ID NO: 23 (i.e., nucleotides GGCTGTCACC). Furthermore, the claims are inclusive of sequences sharing any level of sequence complementarity to the oligonucleotides SEQ ID NO: 2, 3, 23 or 24 and the primers of Myers share some level of sequence complementarity with said oligonucleotides. Myers does not teach incorporating a T7 polymerase promoter sequence into said primers.

Kievits teaches methods for amplifying nucleic acids by an isothermal enzymatic process referred to as NASAB. In this method, the primers are modified to include, at their 5' terminus, a T7 polymerase promoter sequence.

In view of the teachings of Kievits, it would have been obvious to one of ordinary skill in the art at the time the invention was made to have modified the primers of Myers so as to have included a T7 polymerase promoter at the 5' terminus in order to have generated primers which could be used to effectively amplify target nucleic acids by the NASAB method.

13. Claim 21 is rejected under 35 U.S.C. 103(a) as being unpatentable over by Myers (GenBank Accession No.G29936).

Myers teaches a primer consisting of 5'-TTTAAACTGGTAGGAAACTAGGTG-3'. The primer comprises at least 10 nucleotides of SEQ ID NO: 26 (i.e., nucleotides TTTAAACTGG). Myers does not teach incorporating a T7 polymerase promoter sequence into said primers.

Kievits teaches methods for amplifying nucleic acids by an isothermal enzymatic process referred to as NASAB. In this method, the primers are modified to include, at their 5' terminus, a T7 polymerase promoter sequence.

In view of the teachings of Kievits, it would have been obvious to one of ordinary skill in the art at the time the invention was made to have modified the primers of Myers so as to have included a T7 polymerase promoter at the 5' terminus in order to have generated primers which could be used to effectively amplify target nucleic acids by the NASAB method.

14. Claims 19, 20, 24, 25 and 26 are rejected under 35 U.S.C. 103(a) as being unpatentable over NCBI (Accession No. M80517) in view of Zhang et al (reference "AQ") and Cheung et al.

This rejection applies to the claims as they are broadly drawn to primers and probes of 10-35 nucleotides comprising 10 mer fragments and sequences complementary or substantially complementary thereto.

NCBI teaches the complete sequence of the EBV genome, including the BARF-1 open reading frame. NCBI does not teach primers and probes from within the BARF-1 open reading frame.

Zhang et al teaches methods for detecting BARF-1 nucleic acids wherein probes to the BARF-1 nucleic acids are utilized. The probes of Zhang comprise the complete BARF-1 sequence and are labeled with a detectable moiety (page 155-156). Zhang teaches that expression of BARF-1 is correlated with the occurrence of lymphomas (see, e.g. Table 2).

Cheung teaches methods for detecting EBV nucleic acids wherein the methods comprise amplifying the EBV nucleic acids using primers in a polymerase chain reaction and then detecting the amplified nucleic acids using a labeled probe. The primers and probes exemplified by Cheung are 19-21 nucleotides in length.

In view of the teachings of Zhang and Cheung, it would have been obvious to one of ordinary skill in the art at the time the invention was made to have generated additional probes to the EBV BARF-1 sequences and to have generated primers for amplifying BARF-1 sequences in order to have provided an effective means for amplifying and detecting the expression of BARF-1 sequences. In the absence of unexpected results, all oligonucleotides from within the BARF-1 open reading frame are considered to provide equally effective primers and probes. Given the high level of skill in the art and the general information in the art as to how to readily generate primers and probes, particularly EBV primers and probes, it would have been obvious to one of ordinary skill in the art and well within the skill of the art at the time the invention was made to have generated primers and probes identical and equivalent to the broadly claimed primers and probes that could be used to amplify and detect BARF-1 expression. Furthermore, it would have been obvious to one of ordinary skill in the art at the time the invention was made to

have packaged the primers and probes in a kit for the benefits of convenience and cost-effectiveness for practioners in the art wishing to analyze BARF-1 expression.

15. Claims 21 and 22 are rejected under 35 U.S.C. 103(a) as being unpatentable over NCBI (Accession No. M80517) in view of Zhang et al (reference "AQ") and Cheung et al and further in view of Kievits.

The teachings of NCBI, Zhang and Cheung are presented above. The combined references do not teach incorporating a T7 polymerase promoter sequence into said primers.

Kievits teaches methods for amplifying nucleic acids by an isothermal enzymatic process referred to as NASAB. In this method, the primers are modified to include, at their 5' terminus, a T7 polymerase promoter sequence.

In view of the teachings of Kievits, it would have been obvious to one of ordinary skill in the art at the time the invention was made to have modified the BARF-1 primers so as to have included a T7 polymerase promoter at the 5' terminus in order to have generated primers which could be used to effectively amplify EBV BARF-1 target nucleic acids by the NASAB method

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Carla Myers whose telephone number is (703) 308-2199. The examiner can normally be reached on Monday-Thursday from 6:30 AM-5:00 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, W. Gary Jones, can be reached on (703)-308-1152. The fax number for the Technology Center is (703)-305-3014 or (703)-305-4242.